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EXAMINER

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WHITE, E

ART UNIT	PAPER NUMBER
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1623

17

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 17

Application Number: 09/118,730

Filing Date: July 17, 1998

Appellant(s): Beavers et al.

William H. Eilberg

For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed May 18, 2000.

Art Unit: 1623

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-8 and 20-23 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) ClaimsAppealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Art Unit: 1623

(10) *Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al (US Patent No. 4,808,576).

Applicants set forth product-by-process claims of a free-acid form of hyaluronic acid made by a method which involves obtaining the free acid form of hyaluronic acid from an alkali-metal salt of hyaluronic acid.

The free acid form of hyaluronic acid is well known in the art as indicated in the Schultz et al patent which discloses hyaluronic acid as being useful in the treatment of irritated or inflamed tissue by remote application wherein the hyaluronic acid may be used in its free acid form (see column 4, lines 5-19). While Applicants's claims are directed to a product limited by the process employed in its production there is no reason found for concluding that the product claimed (e.g., free acid from of hyaluronic acid) could be distinguished from the free acid form of hyaluronic acid of the Schultz et al's patent merely because the claimed product was produced under the specific conditions recited, which conditions fall within the purview of the disclosure of the Schultz et al's patent. Accordingly, it would have been obvious to one of ordinary skill in the art having the Schultz et al patent before him to employ a free acid form of hyaluronic acid of the instant claims in view of their closely related structures and the resulting expectation of similar therapeutic properties.

Applicants are reminded that process limitations cannot impart patentability to a product which is not patentably distinguished over the prior art. *In re Thorpe et al.* (CAFC 1985), *supra*; *In re Dike* (CCPA 1968) 394 F2d 584, 157 USPQ 581; *Tri-Wall Containers, Inc. v. United States et al.* (Ct Cls 1969) 408 F2d 748, 161 USPQ 116; *In re Brown et al.* (CCPA 1972) 450 F2d 531, 173 USPQ 685; *Ex parte Edwards et al.* (BPAI 1986) 231 USPQ 981.

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(11) Response to Argument

The Merck Index, 12th Edition, 1996, Abstract No. 4793, pages 813 and 814 (attached hereto), is disclosed to provide background information for hyaluronic acid. The Merck Index characterized hyaluronic acid as having a molecular weight within the range of 50,000 to 8×10^6 depending on source, methods of preparation and determination; a natural high viscosity mucopolysaccharide with alternating β (1-3) glucuronidic and β (1-4) glucosaminidic bonds (see the structure hyaluronic acid on page 813 of the Merck Index); found in the umbilical cord, in vitreous humor, in synovial fluid, in pathologic joints, in group A and C hemolytic streptococci and in Wharton's jelly; used as a surgical aid (ophthalmological) and adjunct in treatment of noninfectious synovitis.

Appellant's arguments filed May 18, 2000 have been fully considered but they are not persuasive. Appellants argue against the rejection of the claims under 35 U.S.C. 103 on the grounds that the terminology used to describe hyaluronic acid in the literature is misleading - when what is really meant is sodium hyaluronate. Appellants argue the Schultz et al patent admits that all the data presented in the patent were based on sodium hyaluronate, not on free hyaluronic acid. However, Schultz does point out at column 4, lines 61 and 62, the use of hyaluronic acid in its free acid form.

Appellants argue that the claims on appeal sets forth a free-acid form of hyaluronic acid which is suitable for placement permanently or temporarily in the body which means that the claimed hyaluronic acid, as described by Appellants, is required to be of "medical grade". The Schultz et al patent clearly meet the "medical grade" limitation since the Schultz et al patent discloses hyaluronic acid that can be administered to mammals by the typical remote routes including intravenous, intramuscular, subcutaneous and topical. See the abstract of the Schultz et al patent wherein the patent discloses treating arthritis in horse or human joints with hyaluronic acid. The molecular weight and viscosity disclosed in the Merck Index cited above and in the

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Schultz et al patent for hyaluronic acid are similar to the molecular weight and viscosity disclosed in the instant application.

On page 13, 2nd paragraph of Appellants Appeal Brief filed May 18, 2000, Appellants admit on record that "it is possible to make free hyaluronic acid by at least one other method, but the result is not of medical grade." It is noted that the instant claims are product-by-process claims which is considered to be a product claim. No limitations have been disclosed on the product claims except for the process limitation for producing the product. The process steps disclosed in the claims have already been allowed in another application. Process limitations cannot impart patentability to a product which is not patentable distinguished over the prior art. Appellants have not claimed a "medical grade" hyaluronic acid that is distinct from the hyaluronic acid of the Schultz et al patent which also reports administering the hyaluronic acid to mammals.

Appellants further argue that the present invention sets forth surprising results. Appellants argue that the fact that Appellants have synthesized a composition which is not available anywhere is itself an unexpected result which merits a patent. This statement is not agreed with in view of the Schultz et al patent.

The three declarations by Dr. Ellington M. Beavers which described the difficulty in obtaining the free acid form of hyaluronic acid from commercial suppliers and explained a process which requires hyaluronic acid in its free form to react with poly-aziridine are acknowledged.

In conclusion, in view of the similar physical attributes of hyaluronic acid (molecular weight, viscosity) and similar utility which involve administering the hyaluronic acid to humans and animals that are disclosed in the cited Merck Index and in the Schultz et al patent, the rejection of the claims under 35 U.S.C. 103 as being unpatentable over the Schultz et al patent should be maintained.

Art Unit: 1623

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

EW
July 28, 2000

Howard C. Lee

Howard C. Lee
Primary Examiner
Art Unit 1623



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SUPERVISORY PATENT EXAMINER
TECH CENTER 1600

Confere

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

TWELFTH EDITION

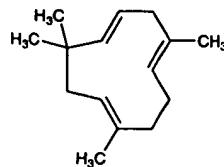
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1996

Moskovitz, *Antimicrob. Ag.*
tion has pH near 6.7, and is
D₅₀ i.p. in mice: 750 mg/kg
ammonium antimony tungsten

4-quinolinol 1-oxide; 2-heptyl-
 $C_{16}H_{21}NO_2$; mol wt 259.35. C
12.34%. Inhibitor of electron
cone bc, segment of the respira-
turally occurring antagonist to
udomonas pyocyanea: Hays et
(1948); J. Lightbown, *J. Gen.
etics*: J. W. Cornforth, A. T.
(1954). Synthesis: *eidem*, *ibid.*
al., *J. Chem. Soc.* 1956, 3079.
ort: J. W. Lightbown, F. L.
(1956); M. Avron, *ibid.* 78, 735.
Volin, *Biochim. Biophys. Acta*
ton permeability of the mito-
ib, M. Wikström, *Biochem. J.*
ibition: G. Izzo et al., *FEBS*
Droppa et al., *Z. Naturforsch.*

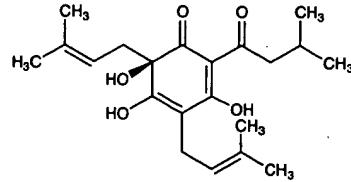


Liquid. bp₅ 106-107°. n_D^{20} 1.5004. N. P. Damodaran, S. Dev, *Tetrahedron* 24, 4113 (1968). Also reported as bp₁₀ 123°. n_D^{25} 1.5015. d_4^{25} 0.8865. R. P. Hildebrand et al., *Chem. Ind. (London)* 1959, 489. NMR spectrum: S. Dev et al., *J. Am. Chem. Soc.* 90, 1246 (1968).

Silver nitrate complex, $C_{15}H_{24}2AgNO_3$, crystals from aq ethanol, mp 175°.

β-Humulene, (E,E)-1,4,4-trimethyl-8-methylene-1,5-cyclo-
undecadiene. Liquid. n_D^{20} 1.5014. d_4^{20} 0.8905.

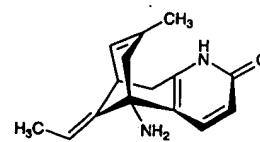
4790. Humulon. (R)-3,5,6-Trihydroxy-4,6-bis(3-methyl-
2-butyl)-2-(3-methyl-1-oxobutyl)-2,4-cyclohexadien-1-one;
α-bitter acid; α-lupulic acid; humulone. $C_{21}H_{30}O_5$; mol wt
362.47. C 69.59%, H 8.34%, O 22.07%. Antibiotic con-
stituent of hops (*Humulus lupulus L.*, *Moraceae*). See also
Lupulon. Isoln from commercial hops: Bungener, *Bull.
Soc. Chim.* [2] 45, 487 (1886); Barth, Lintner, *Ber.* 31, 2022
(1898); Wolmer, *Ber.* 49, 780 (1916); Lewis et al., *J. Clin.
Invest.* 28, 916 (1949). Structure: Riedl, *Ber.* 85, 692
(1952); Carson, *J. Am. Chem. Soc.* 73, 4652 (1951). Ab-
solute configuration and structure of preferred isomer: De-
Keukeleire, Verzele, *Tetrahedron* 26, 385 (1970).



Crystals from ether, mp 65-66.5°. Bitter taste, esp in
alcoholic soln. More stable to air than lupulon. Monobasic
acid. $[\alpha]_D^{20}$ -212° (1.0 g in 15.5 g 96% alc). uv max (ethanol):
237, 282 nm (ϵ 13,760; 8330). Soluble in the usual
organic solvents. Slightly sol in boiling water from which it
separates as a milky precipitate on cooling. Forms a sodium
salt which is readily sol in water. Suffers no loss of
bacteriostatic potency against *Staphylococcus aureus* upon
autoclaving 40 ppm in phosphate buffer at pH 6.5 or 8.5.
The presence of ascorbic acid in low concns extends the
duration of bacteriostatic action.

4791. Huperzine A. [5R-(5a,9b,11E)]-5-Amino-11-
ethylidene-5,6,9,10-tetrahydro-7-methyl-5,9-methanocyclo-
octa[b]pyridin-2(1H)-one; selagine; HUP. $C_{15}H_{18}N_2O$; mol
wt 242.32. C 74.35%, H 7.49%, N 11.56%, O 6.60%. Re-
versible alkaloid inhibitor of AChE which crosses the
blood-brain barrier. Occurs as the (-)-form in the vegeta-
tive part of clubmosses; teas brewed from these mosses have
traditionally been used in China to alleviate memory prob-
lems. Isolated as selagine from *Lycopodium selago L.*, *Lycopodiaceae*: J. Muszynski, *Quart. J. Pharm. Pharmacol.* 21,
34 (1948); from *Huperzia serrata* as huperzine: Chin. Co-op
Res. Group, *J. Tradit. Chin. Med.* 2, 45 (1982). Original
structure: Z. Valenta et al., *Tetrahedron Letters* 1960, 26;
revised structure as huperzine A: J.-S. Liu et al., *Can. J. Chem.* 64, 837 1986. Identity with selagine: W. A. Ayer et al., *ibid.* 67, 1538 (1989). Synthesis of (+)-form: A. P. Kozikowski et al., *J. Org. Chem.* 56, 4636 (1991); G. Campani et al., *ibid.* 58, 7660 (1993). NMR spectra: B. N. Zhou et al., *Phytochemistry* 34, 1425 (1993). Anticholin-
esterase activity: Y.-E. Wang et al., *Acta Pharmacol. Sin.* 7,
110 (1986); binding profile of enantiomers: M. McKinney et al., *Eur. J. Pharmacol.* 203, 303 (1991); binding specificity: Y. Ashani et al., *Mol. Pharmacol.* 45, 555 (1994). Clinical evaluation in senile dementia: R.-W. Zhang et al., *Acta Pharmacol. Sin.* 12, 259 (1991). Brief review of chemistry

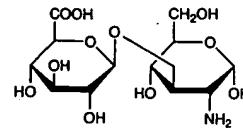
and clinical use: D. Bai, *Pure Appl. Chem.* 65, 1103-1112
(1993).



Monoclinic crystals from acetone, mp 214°-215°. $[\alpha]_D^{20}$
-147° (c = 0.36 in CH_3OH) (Ayer). Also reported as mp
230°. $[\alpha]_D^{25}$ -150.4° (c = 0.498 in $MeOH$) (Liu). uv max
($EtOH$): 231, 313 nm ($\log \epsilon$ 4.01, 3.89).

THERAP CAT: In treatment of memory disorders.

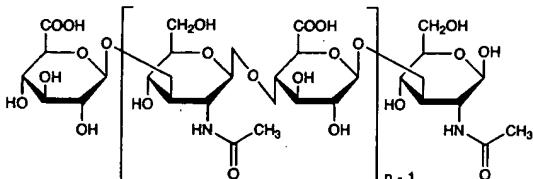
4792. Hyalobiuronic Acid. 2-Amino-2-deoxy-3-O-β-D-
glucopyranuronosyl-β-D-glucoside. $C_{12}H_{21}NO_{11}$; mol wt
355.30. C 40.57%, H 5.96%, N 3.94%, O 49.53%. Disac-
charide unit of hyaluronic acid. Isoln from hyaluronic acid:
Rapport et al., *Nature* 168, 996 (1951). Structure: Weiss-
man, Meyer, *J. Am. Chem. Soc.* 76, 1753 (1954). Synthesis:
Takanashi et al., *ibid.* 84, 3029 (1962).



Rectangular prisms from water, darken at 190° with no
characteristic melting or dec point. pK_1' = 2.6, pK_2' = 7.1. Shows mutarotation: $[\alpha]_D^{20}$ +34° → +30° (c = 1.08 in
0.1N HCl). Sparingly sol in hot water, dilute HCl, dil
 $NaHCO_3$. Practically insol in water, glacial acetic acid,
ethanol, methanol and pyridine.

N-Acetylhyalobiuronic acid, $C_{14}H_{23}NO_{12}$, amorphous.
 pK' = 3.3. $[\alpha]_D^{24}$ -32° (c = 2.0 in water).

4793. Hyaluronic Acid. Mol wt is within the range of
50,000 to 8×10^6 depending on source, methods of prepn.
and determination. A natural high viscosity mucopolysac-
charide with alternating β (1-3) glucuronicid and β (1-4)
glucosaminidic bonds. Found in the umbilical cord, in
vitreous humor, in synovial fluid, in pathologic joints, in
group A and C hemolytic streptococci and in Wharton's
jelly. Isoln and characterization: Meyer, Palmer, *J. Biol.
Chem.* 107, 629 (1934); 114, 689 (1936); Balazs, *Fed. Proc.*
17, 1086 (1958); Laurent et al., *Biochim. Biophys. Acta* 42,
476 (1960). Structure: Weissman, Meyer, *J. Am. Chem.
Soc.* 76, 1753 (1954); Meyer, *Fed. Proc.* 17, 1075 (1958).
Crystal structure of hyaluronate films: Dean et al., *Science*
179, 560 (1973); Atkins, Sheehan, *ibid.* 562. Possible role in
determining blood vessel location in the embryo: R. N.
Feinberg, D. C. Beebe, *Science* 220, 1177 (1983). Reviews:
Tauber, *Chemistry and Technology of Enzymes* (New York,
1946); Meyer, Rapport in *Advan. Enzymol.* 13, 199 (1952);
Whistler, Olson in *Advan. Carbohyd. Chem.* 12, 299 (1957).
Review of role in various developmental-processes: B.-P.
Toole, *Cell Biology of Extracellular Matrix*, E. D. Hay, Ed.,
(Plenum Press, New York, 1981) pp 259-288.



Sodium salt, ARTZ, Connnettivina, Equron, Healon, Healonid,
Hyacid, Hyalgan, Hyalovet, Hyonate, Ial, Opegan, Pro-
visc, Synacid. $[\alpha]_D^{25}$ -74° (c = 0.25 in water): Rapport et al.,
J. Am. Chem. Soc. 73, 2416 (1951). Most viscosity
determinations of hyaluronic acid vary from 1-8: Jensen,

Acta Chem. Scand. **7**, 603 (1953). Infrared absorption spectra: Orr, *Biochim. Biophys. Acta* **14**, 173 (1954).

USE: Surgical aid (ophthalmological).

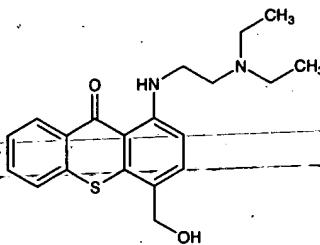
THERAP CAT (VET): Adjunct in treatment of noninfectious synovitis.

4794. Hyaluronidases. Spreading factor; diffusing factor; invasin; Alidase; Apertase; Diffusin; Enzodase; Harodase; Hyalase; Hyalozima; Hyalidase; Hyasmonta; Hyason; Hyazyme; Infiltrase; Jalovis; Kinaden; Kinetin; Luronase; Permease; Rondase; Ronidase; Thiomucase; Unidasa; Wydase. Enzymes which have in common the cleavage of glycosidic bonds of hyaluronic acid, q.v., and, to a variable degree, of some other acid mucopolysaccharides of connective tissue. The skin is probably the largest store of hyaluronidase in the body; the enzyme although generally present in an inactive form, may be supposed to regulate the velocity of water and metabolite exchange by decreasing the viscosity of the intercellular matrix. Also has a physiological role in fertilization: The sperm is rich in the enzyme and can thus advance better in the cervical canal and reach the ovum. Found in the type II pneumococci, in group A and C hemolytic streptococci, *Staphylococcus aureus* and *Clostridium welchii*: Linker *et al.*, *J. Biol. Chem.* **219**, 13 (1956); in heads of leeches: Linker *et al.*, *Nature* **180**, 810 (1957); in snake venoms: Favilli, *ibid.* **145**, 866 (1940); in testes: Hahn, *Biochem. Z.* **315**, 83 (1943); Höglberg, *Acta Chem. Scand.* **8**, 1098 (1954). Biochemical properties: D. Platt, *Arzneimittel-Forsch.* **20**, 1836 (1970). Review: Meyer, Report in *Advan. Enzymol.* **13**, 199-236 (1952); Meyer *et al.*, *The Enzymes* vol. 4, P. D. Boyer *et al.*, Eds. (Academic Press, New York, 2nd ed., 1960) pp 447-460; Meyer, *ibid.* vol. 5 (3rd ed., 1971) pp 307-320. Reviews of clinical trials in myocardial infarction: G. S. May *et al.*, *Progr. Cardiovasc. Dis.* **25**, 335-359 (1983); A. B. Saunders, *Emerg. Med. Clin. North Am.* **6**, 361-372 (1988). Hyaluronidase manufacturers define their product in terms of turbidity-reducing (TR) units or in viscosity units. Prepd solns for injection usually contain 150 turbidity-reducing units or 500 viscosity units dissolved in 1 ml of isotonic NaCl soln.

USE: Pharmaceutical aid (diffusing agent—s.c. injections).
THERAP CAT: Spreading agent.

THERAP CAT (VET): To promote diffusion, absorption, re-sorption.

4795. Hycanthone. *1-[2-(Diethylamino)ethyl]amino-4-(hydroxymethyl)-9H-thioxanthen-9-one.* $C_{20}H_{24}N_2O_2S$; mol wt 356.49. C 67.38%, H 6.79%, N 7.86%, O 8.98%, S 8.99%. Metabolite of lucanthone, q.v.: Rosi *et al.*, *Nature (London)* **208**, 1005 (1965). Prepn by oxidative fermentation of lucanthone and schistosomicidal activity: Rosi *et al.*, *J. Med. Chem.* **10**, 867 (1967); Neth, pat. Appl. 6,410,359, and Rosi, Peruzzotti, U.S. pats. 3,294,803; 3,312,598 (1965, 1966, 1967 all to Sterling Drug). Alternate synthesis: Laidlaw *et al.*, *J. Org. Chem.* **38**, 1743 (1973).



Crystals, mp 100.6-102.8°. Absorption max (ethanol): 233, 258, 329, 438 nm (ϵ 19400, 37000, 9700, 6600). Extremely sensitive to acid.

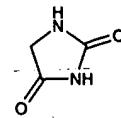
Hydrochloride, mp 173-176° (dec).

Mesylate, *Etenol*.

THERAP CAT: Antihelmintic (Schistosoma).

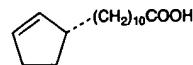
4796. Hydantoin. *2,4-Imidazolidinedione; 2,4-(3H,5H)-imidazoledione; glycolylurea.* $C_3H_4N_2O_2$; mol wt 100.08. C 36.01%, H 4.03%, N 27.99%, O 31.97%. Prepn: Baeyer, *Ann.* **130**, 129 (1864). Manuf: Gresham, Schweitzer, U.S. pat. 2,402,134 (1946 to du Pont); White, Wysong,

U.S. pat. 2,663,713 (1953 to Dow). Review: J. H. Bamforth in Kirk-Othmer *Encyclopedia of Chemical Technology*, 12 (Wiley-Interscience, New York, 3rd ed., 1980) pp 121-122.



Needles from methanol, mp 220°. Slightly sol in water; sol in alcohol, in solns of fixed alkali hydroxides.

4797. Hydnocarpic Acid. *(R)-2-Cyclopenten-1-decanoic acid; 11-(2-cyclopenten-1-yl)undecanoic acid.* H_28O_2 ; mol wt 252.40. C 76.14%, H 11.18%, O 12.34%. Component of chaulmoogra oil; naturally occurring form. Isoln from seeds of *Hydnocarpus wightiana* Blume, *H. antehelmintica* Pierre, *Flacourtiaceae*, or from the seeds of *Taraktogenos kurzii* King, *Bixaceae*; F. B. Power, M. H. Wcliffe, *J. Chem. Soc.* **87**, 884 (1905); *ibid.* **91**, 557 (1907). Structure: R. L. Shriner, R. Adams, *J. Am. Chem. Soc.* **72**, 2727 (1920). Synthesis of *dl*-hydnocarpic acid: D. G. Diaper, J. C. Smith, *Biochem. J.* **42**, 581 (1948). *Tom's Handbook of Toxicology*, vol. 1, W. S. Spector, Ed. (W. B. Saunders, Philadelphia, 1956) pp 274-275. Antimicrobial spectrum: P. L. Jacobsen, L. Levy, *Proc. West. Pharmacol. Soc.* **15**, 44 (1972). Mechanism of action: *eidem*, *Antimicrob. Chemother.* **3**, 373 (1973). Chromatographic determination of oil: W. W. Christie *et al.*, *Lipids* **24**, 116 (1989).



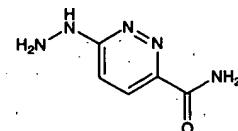
Colorless, glistening leaflets from petr ether + ethyl acetate, mp 59-60°. $[\alpha]_D^{25} +68.3^\circ$ (chloroform). Sparingly sol in usual organic solvents; sol in chloroform.

dl-Form, pearly plates from alcohol, ethyl acetate + ethyl ether + ethyl acetate, mp 59-59.5°.

Sodium salt, *sodium hydnocarpate, hydnocarpate sodium gynocardate*. Yellowish powder. Sol in water. The aq soln is alkaline. MLD i.v. in rats: 100-125 mg (Spector).

THERAP CAT: Antibacterial (leprostatic).

4798. Hydracarbazine. *6-Hydrazino-3-pyridazinecarboxamide; 3-hydrazino-6-carbamoylpyridazine; 3-hydrazino-6-carboxamide.* $C_8H_8N_2O$; mol wt 153.18. C 39.21%, H 4.61%, N 45.73%, O 10.45%. Prepn: Léonard, Rouaix, *Bull. Soc. Chim. France* **1959**, 1793; *Brit. pat.* **409** (1960 to Chimie et Atomistique).



Crystals, dec 249-250°.

Note: A component of *Normatensyl*.

THERAP CAT: Antihypertensive; diuretic.

4799. Hydrylic Acid. *3-Hydroxypropanoic acid; hydroxypropionic acid; ethylene lactic acid.* $C_3H_6O_3$; mol wt 90.08. C 40.00%, H 6.71%, O 53.28%. Prepn: COOH. Prepd by alkaline hydrolysis of the nitrile. *Read, Org. Syn. coll. vol. I*, 321 (2nd ed., 1941).

Viscous liq. Strong acid, pK (25°): 4.51. On dilution with 50% H_2SO_4 dec into water and acrylic acid.

Very sol in water, sol in alcohol, miscible with ether.

Sodium salt, $NaC_3H_5O_3$, deliquescent crystals, mp 140-145°; freely sol in cold water.

4800. Hydralazine. *1(2H)-Phthalazinone hydrochloride; 1-hydrazinophthalazine; Ciba 5968; Práparat 5968; Hippofotalin; Hypophthalin; Apresoline.* $C_8H_8N_2$; mol